CME

Depression during pregnancy

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ABSTRACT

OBJECTIVE To review existing literature on depression during pregnancy and to provide information for family physicians in order to promote early detection and treatment.

QUALITY OF EVIDENCE MEDLINE was searched from January 1989 through August 2004 using the key words depression, pregnancy, prenatal, and antenatal. Articles focusing on depression during pregnancy were chosen for review; these articles were based on expert opinion (level III evidence) and prospective studies (level II evidence).

MAIN MESSAGE Pregnancy does not safeguard women against depressive illness. The Edinburgh Postnatal Depression Scale is an effective screening tool for identifying women with depressive symptoms during pregnancy. Once diagnosed with major depression, these patients need to be monitored closely for up to a year after delivery. Patients with mild-to-moderate illness should be referred for psychotherapy. More severely ill patients might require additional treatment with antidepressants. The most commonly used antidepressants are selective serotonin reuptake inhibitors and the serotonin and norepinephrine reuptake inhibitor, venlafaxine. For each patient, risk of treatment with an antidepressant needs to be compared with risk of not treating her depressive illness.

CONCLUSION Early detection of depression during pregnancy is critical because depression can adversely affect birth outcomes and neonatal health and, if left untreated, can persist after the birth. Untreated postpartum depression can impair mother-infant attachments and have cognitive, emotional, and behavioural consequences for children.

RÉSUMÉ

OBJECTIF Recenser les publications traitant de la dépression chez la femme enceinte et donner au médecin de famille l'information nécessaire pour mieux déceler et traiter cette condition.

QUALITÉ DES PREUVES Une recherche a été effectuée dans MEDLINE entre janvier 1989 et août 2004 à l'aide des mots-clés *depression, pregnancy, prenatal,* et *antenatal*. Les articles centrés sur la dépression durant la grossesse ont été retenus pour analyse; ces articles reposaient sur l'opinion d'experts (preuves de niveau III) et sur des études prospectives (preuves de niveau II)

PRINCIPAL MESSAGE Les femmes enceintes ne sont pas à l'abri des troubles dépressifs. L'échelle de dépression postnatale d'Édinbourg est un outil efficace pour identifier les femmes qui présentent des symptômes dépressifs durant la grossesse. En cas de dépression sévère, la femme devra être suivie de près jusqu'à un an après l'accouchement. Les cas de dépression légère à modérée devraient être dirigés en psychothérapie. Les dépressions plus graves pourraient exiger l'usage d'antidépresseurs. Les plus couramment utilisés sont les inhibiteurs sélectifs du recaptage de la sérotonine et l'inhibiteur du recaptage de la noradrénaline et de la sérotonine, la venlafaxine. Dans chaque cas, le risque lié à l'utilisation de l'antidépresseur doit être comparé à celui de ne pas traiter la dépression.

CONCLUSION Il est crucial de déceler la dépression tôt durant la grossesse; en effet, cette maladie peut affecter négativement l'issue de la grossesse et la santé néonatale; non traitée, elle peut se prolonger au-delà de l'accouchement. Une dépression postnatale peut interférer avec le développement des liens mère-enfant et avoir des conséquences cognitives, émotionnelles et comportementales pour l'enfant.

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There is growing evidence to challenge the notion that pregnancy protects patients from mental illness. Rates of depression during pregnancy have been reported to be as high as 20%.[1] Evidence suggests that postpartum depression (PPD) can be part of a continuum, with onset of illness during pregnancy.[1-3] Family physicians are often the first caregivers to come into contact with pregnant women; they, therefore, have a unique opportunity to monitor women's moods over several weeks. Early detection of symptoms could facilitate timely treatment and prevent ongoing depression. This article was written to assist family physicians in recognizing prenatal depression and to aid their decision making for managing this complex condition.

Quality of evidence

MEDLINE was searched from January 1989 through August 2004 using the key words depression, pregnancy, prenatal, and antenatal. Articles were also gathered from the references of papers generated by the initial search. For this article, the search was limited to English-language human studies; articles focusing on depression during pregnancy were chosen for review. The articles were based on expert opinion (level III evidence) and prospective studies (level II evidence). There are few trials offering level I evidence in this area due to ethical restrictions on extracting data on pregnant populations. Available data have been incorporated into this review.

Course of depression during pregnancy

Diagnosis of major depression is often made by mental health professionals during structured clinical interviews using criteria described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR).[4] For family physicians facing time constraints, one of the quickest ways to assess pregnant women's moods is through responses to self-reported questionnaires in conjunction with objective questions to assess mood.

Screening methods, such as the Edinburgh Postnatal Depression Scale (EPDS) (**Figure 1**),[5] have been developed for assessing postpartum depression. As yet, no screening tools are specifically designed for assessing antenatal depression. Murray and Cox[6] investigated use of the EPDS during pregnancy and found that it was effective at identifying women with major depression (level II evidence). The EPDS is commonly used in research to detect perinatal mood disorders.[7-9] Because the EPDS is only a screening tool, high scores do not in themselves confirm diagnosis of depression. A score above 12 indicates probable depressive disorder.[6,7] Other self-rating screening tools, such as the Beck Depression Inventory (BDI),[10] tend to focus on somatic symptoms and, therefore, make detection of depression during pregnancy difficult. We need screening tools that take into account the overlap between symptoms of pregnancy and symptoms of depression.

During the first trimester, it can be particularly difficult to diagnose depression because of this overlap. Bennett et al[9] reported a rate of depression of 7.4% during the first trimester. During the second trimester, this figure rose to 12.8% and remained at 12% during the third trimester (level I evidence). In a longitudinal study, Josefsson et al[8] examined rates of depression during late pregnancy and reported

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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Figure 1. Edinburgh Postnatal Depression Scale

INSTRUCTIONS FOR USERS

1. The mother is asked to underline the response that comes closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother's discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.

Name: _____ Baby's age: _____
Address: _____

Please UNDERLINE the answer that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

I have been able to laugh and see the funny side of things.
- 0 As much as I always could
- 1 Not quite so much now
- 2 Definitely not so much now
- 3 Not at all

I have looked forward with enjoyment to things.
- 0 As much as I ever did
- 1 Rather less than I used to
- 2 Definitely less than I used to
- 3 Hardly at all

*I have blamed myself unnecessarily when things went wrong.
- 3 Yes, most of the time
- 2 Yes, some of the time
- 1 Not very often
- 0 No, never

I have been anxious or worried for no good reason.
- 0 No, not at all
- 1 Hardly ever
- 2 Yes, sometimes
- 3 Yes, very often

*I have felt scared or panicky for no very good reason.
- 3 Yes, quite a lot
- 2 Yes, sometimes
- 1 No, not much
- 0 No, not at all

*Things have been getting on top of me.
- 3 Yes, most of the time I haven't been able to cope at all
- 2 Yes, sometimes I haven't been coping as well as usual
- 1 No, most of the time I have coped quite well
- 0 No, I have been coping as well as ever

*I have been so unhappy that I have had difficulty sleeping.
- 3 Yes, most of the time
- 2 Yes, sometimes
- 1 Not very often
- 0 No, not at all

*I have felt sad or miserable.
- 3 Yes, most of the time
- 2 Yes, quite often
- 1 Not very often
- 0 No, not at all

*I have been so unhappy that I have been crying.
- 3 Yes, most of the time
- 2 Yes, quite often
- 1 Only occasionally
- 0 No, never

*The thought of harming myself has occurred to me.
- 3 Yes, quite often
- 2 Sometimes
- 1 Hardly ever
- 0 Never

**Items are reverse scored (ie, 3, 2, 1, 0). Responses are scored 0, 1, 2, and 3 according to increased severity of symptoms. Total score is calculated by adding the scores for each of the 10 items. Scores >12 identify patients at risk for postpartum depression.*
Figure reproduced from Cox et al.[5] Users may reproduce the scale without further permission providing they respect copyright by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.

rates of 17%. When patients were followed into the postpartum period, rates were found to have decreased to 13% by 6 to 8 weeks after the birth (level II evidence). Evans et al[7] followed a group of women through pregnancy to the postpartum period and found that levels of depression during pregnancy were comparable to those reported during the postpartum period (level II evidence).

Gotlib and colleagues[1] were among the first to point out a continuum of depression through pregnancy and into the postpartum period (level II evidence). Despite their observation, research during the past 25 years has focused on postpartum depression, rendering pregnancy-related depression a secondary issue. While the DSM-IV-TR recognizes postpartum-onset mood disorders, it does not make any reference to depression during pregnancy.

Only during the last 4 years have we seen depression during pregnancy resurface as an area of importance in the literature. This is due in part to the increase in referrals of depressed pregnant patients to reproductive psychiatry programs. This increase might reflect patients' increasing willingness to report symptoms to their primary caregivers or a heightened awareness among physicians of the onset

of illness during pregnancy. The fact that depression, if left undiagnosed, can persist throughout pregnancy into the postpartum period is gaining widespread recognition today (level II evidence).[1,2,7,8]

Risk factors

Many studies have delineated the risk factors associated with depression during pregnancy; risk factors are summarized in **Table 1**. Personal and family history of depression are substantial biologic risk factors (level II evidence).[11,12] Major psychosocial risk factors are history of childhood abuse, domestic violence or marital conflict, substance abuse or smoking, inadequate social support, single motherhood, lower educational levels, and unemployment (level II evidence).[1,11,13-16]

Table 1. Summary of risk factors for developing depression during pregnancy

BIOLOGIC
History of mood and anxiety disorders
History of postpartum depression
History of premenstrual dysphoric disorder
Family history of psychiatric illness
PSYCHOSOCIAL
History of childhood abuse
Younger age
Unplanned pregnancy
Ambivalence or negative feelings about the pregnancy
Single motherhood
Greater number of children
Limited social support
Domestic violence or marital conflict
Low level of education and unemployment
Substance abuse and smoking

Once at-risk patients have been identified, they can be monitored throughout pregnancy for early signs of illness, whether it is new onset, exacerbation, or relapse of an existing depression.

Treatment

Interventions for depression during pregnancy most commonly include antidepressant medications; psychotherapy (individual or group); bright-light therapy; and very rarely, electroconvulsive therapy (ECT).

The two most commonly used psychotherapies are interpersonal therapy (IPT), which focuses on improving social interactions and coping with life transitions, and cognitive behavioural therapy (CBT), which aims to adjust patients' self-defeating thought patterns. Using IPT during pregnancy has been shown to improve mood substantially after 16 weeks (level I evidence).[17] Unfortunately, there is little research on the effectiveness of other non-pharmacologic treatments for prenatal depression. Although the effectiveness of CBT for PPD has been demonstrated (level I evidence),[18] to date there is no research on its use for depression during pregnancy. The effectiveness of group therapy for depression during pregnancy has not been reported, although antenatal group therapy has been shown to be effective in preventing PPD (level II evidence).[19]

Pharmacologic treatment. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), are most commonly used today. The older antidepressants, like the tricyclic antidepressants, are no longer used routinely as first-line treatment for major depression. The SSRIs include fluoxetine (eg, Prozac), paroxetine (Paxil), sertraline (eg, Zoloft), fluvoxamine (eg, Luvox), and citalopram (Celexa). Venlafaxine is an example of a SNRI antidepressant. Bupropion (eg, Wellbutrin) and mirtazapine (Remeron) are among the newer dual-action antidepressants we are seeing in pregnant women. All SSRIs, as well as venlafaxine (Effexor), have been found to cross the placenta. Paroxetine and sertraline pass through the placenta more slowly than fluoxetine (level II evidence),[20] but this finding must be interpreted with caution in clinical practice. If a patient has responded best to fluoxetine, for example, it is recommended that she continue taking fluoxetine throughout pregnancy. Because every mother and baby metabolize medication differently, no universal statement about the choice of a particular medication during pregnancy can be made. **Table 2**[21-38] summarizes research findings on SSRI and SNRI exposure during pregnancy.

When a woman is treated with antidepressants during pregnancy, both mother's and doctor's concerns relate to the risk of teratogenesis, neonatal

Table 2. Summary of research findings on the safety of taking antidepressants during pregnancy: *There was no increased risk of teratogenicity with any of the medications.*

MEDICATION (NO. OF BABIES EXPOSED)	OBSTETRIC COMPLICATIONS AND NEONATAL WITHDRAWAL	LONG-TERM EFFECTS
Fluoxetine[21-27] (1532)	Third trimester: premature delivery or perinatal complications; higher doses might lead to low birth weight; transient withdrawal symptoms*	No long-term adverse effects; children of depressed mothers did not have cognitive and language difficulties
Sertraline[24,25,28-30] (234)	Transient withdrawal symptoms*	Further research required
Paroxetine[24,25,28,30,31] (313)	Transient withdrawal symptoms*	Further research required
Citalopram[22-24,30,32,33] (318) Swedish birth registry (375); Lundbeck Safety Database (100)	None	Further research required
Fluvoxamine[28-30] (30)	None	Further research required
Venlafaxine[24,29,34] (174)	Transient withdrawal symptoms*	Further research required
Mirtazapine[35,36] (9)	None	Further research required
Bupropion[37] (534)	None	Further research required
Trazodone[38] (58) Nefazodone[38] (89)	None	Further research required

**Transient neonatal withdrawal symptoms include respiratory distress, jaundice, jitteriness, increased fussing, tremors, and increased crying.*

toxicity, and long-term effects on child development.[39] During the first trimester, the main concern is malformation of the fetus, although there is no current evidence that SSRIs or venlafaxine cause increased teratogenicity (level I evidence).[28,40,41] Concerns in the third trimester focus on neonatal withdrawal because third-trimester exposure to antidepressants has been correlated with higher risk of adverse effects in neonates, such as respiratory distress, feeding difficulties, and low birth weight. These effects, however, have been shown to be transient (level I evidence).[23-25] Although there is little evidence from research, no long-term adverse effects from prenatal exposure to SSRIs or venlafaxine have been reported (level II evidence).[26,27,42] This area requires ongoing research.

A mother's mood should be monitored very closely throughout pregnancy, particularly in the third trimester, where somatic changes might lead to fluctuating dose requirements (level II evidence).[43,44] In a recent study, pharmacologically undertreated maternal mood disorders during the third trimester were found to contribute to poor neonatal adaptation (level II evidence).[45]

Health Canada recently issued a caution about use of SSRIs during the third trimester. Although mothers and doctors might be concerned about exposure, rapid discontinuation of medications is not recommended because it can substantially increase risk of relapse (level II evidence).[46] It is always important to inform obstetricians and neonatologists about exposure to SSRIs in utero so that babies can be closely monitored during delivery and receive appropriate treatment, if necessary.

Among the more than 400 case reports on short- and long-term effects of exposure to tricyclic medications during pregnancy, few major adverse effects have been reported.[47,48] In spite of this, because of their side effect profile, tricyclics are used less frequently today. Monoamine oxidase inhibitors are not recommended during pregnancy.

Nonpharmacologic biologic treatments. Bright-light therapy could be an alternative to pharmacologic intervention and has been shown to be effective for treating antenatal depression (level II and III evidence).[49,50] It is particularly helpful for patients who report seasonal variation in their moods and who do not want to use antidepressants during pregnancy.

Several case reports have shown ECT to be relatively safe and effective during pregnancy (level II evidence).[51-53] The American Psychiatric Association, however, has strict guidelines for administration of ECT[54]: it should be used only when women are severely psychotic or acutely suicidal and when other therapies or medications have clearly failed.

Treatment of depression during pregnancy requires patients and physicians to make collaborative decisions. Each treatment needs to be chosen on a case-by-case basis. For example, women with

a history of recurrent depressive episodes, who are already taking medication at conception, should be encouraged to continue the medication through pregnancy to the postpartum period. If a patient has a history of severe depression and experiences a relapse during her current pregnancy, recommencing treatment with an antidepressant to which she has responded favourably in the past is recommended. For patients who are experiencing an initial depressive episode during pregnancy, treatment with an antidepressant is recommended only if the depression is severe and unlikely to respond to psychotherapy.

The benefits of treating depression during pregnancy far outweigh the consequences that can result from undiagnosed and untreated depression. Maternal psychiatric illness is associated with poor prenatal behaviour, including low attendance at prenatal checkups and increased substance use (level II evidence).[55,56] Adverse obstetric and neonatal outcomes, such as increased preterm delivery, low birth weight, and admission to neonatal nurseries, have also been linked to depression during pregnancy (level II evidence).[57-60] If depression persists into the postpartum period, it can have long-term consequences for both mother and baby. Mothers might go on to develop chronic mood disorders, and untreated postpartum depression can impair mother-infant attachment (level I evidence).[61,62] Finally, being exposed to a chronically depressed mother can have cognitive, emotional, and behavioural consequences for a child (level II evidence).[63-65]

Conclusion

Early detection and treatment of antenatal depression is vital. Once diagnosis is confirmed, family physicians need to include patients in a risk-benefit analysis and carefully outline the consequences of untreated depression for both mother and baby. For mild-to-moderate depression, nonpharmacologic treatments should be offered first, along with referral to a psychologist, if available. For more seriously ill patients, psychotherapy alone might be insufficient, and additional treatment with an antidepressant might be required.

Family physicians might not feel comfortable treating seriously depressed women during pregnancy. Mothers themselves might want a specialist involved in the hope of avoiding taking medications during pregnancy or of learning more about the safety of using medications during pregnancy. Referral to a psychiatrist for expert opinion and ongoing treatment should be considered.

Most research to date supports favourable outcomes for women and babies exposed to antidepressants during pregnancy (level II and III evidence).[66] It is clear now that comprehensive treatment plans must include not only patients and their doctors, but also where applicable, women's partners, obstetricians, neonatologists, and other caregivers (eg, midwives, counselors). Once treatment has been started, it is critical to monitor and follow up into the postpartum period to prevent relapse. In the last 25 years, we have learned much about postpartum depression. We hope the gains made in this area will help us better understand depression during pregnancy.

Competing interests

None declared

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EDITOR'S KEY POINTS

- Pregnancy is a high-risk time for new-onset or reactivated depression; if untreated, depression can continue into the postpartum period.
- A history of depression, especially postpartum depression, is a risk factor for reactivation of mood disorders during pregnancy and afterward.
- For mild-to-moderate depression, psychotherapy might be sufficient. For severe illness, antidepressant medications are recommended and safe. Medication decisions should be made on a case-by-case basis in consultation with each patient.
- Neonatal withdrawal effects are transient, and the effects of untreated depression are of more concern than neonatal exposure to the medication.

POINTS DE REPÈRE DU RÉDACTEUR

- Durant la grossesse, le risque de développer ou de réactiver une dépression est accru; sans traitement, la dépression peut se prolonger durant le postpartum.
- Une dépression antérieure, notamment durant le postpartum, augmente le risque d'une réactivation des troubles de l'humeur durant la grossesse
- Dans les cas légers à modérés, la psychothérapie pourrait suffire. Pour une dépression sévère, l'usage d'antidépresseurs est recommandé et sécuritaire. L'option pharmacologique doit être individualisée et discutée avec la patiente.
- Les effets du sevrage néonatal sont transitoires; ceux d'une dépression non traitée sont plus préoccupants que l'exposition du nouveau-né à la médication.

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